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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/241,595	02/02/1999	JORG REIMANN	9325-0008.30	8928

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BROWDY AND NEIMARK
624 Ninth Street, N.W.
Washington, DC 20001

EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/241,595	Applicant(s) REIMANN ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2002 and 28 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11 and 13-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 13-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments and responses received on 2/12/02 and 3/26/02 have been entered. Claims 2 and 12 have been canceled. New claim 31 has been added. Claims 1, 3-11, and 13-31 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1, 3-5, 7-8, 10-11, 13, 16-17, 20-21, 23, and 25-30 under 35 U.S.C. 112, first paragraph, for lack of written description is withdrawn in view of applicant's arguments and evidence in the form of printed publications.

The rejection of pending claims 1, 3-11, and 13-31 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in part. Applicant's arguments have been fully considered but have not been considered persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the specification provides sufficient guidance for entrapping both hydrophilic or hydrophobic proteins or molecules within HBsAg particles. Specifically, the applicant argues that the specification teaches that HBsAg particles are hollow and further contain pores in the phospholipid /protein layers. The previous office action, however, stated that the specification does not provide an enabling disclosure for making HBsAg particles which non-covalently contain inside the particles any biologically active protein. The specification discloses that the HBsAg particles are incubated with the protein, either the antigen, cytokine, or bacterial toxin, such that the protein is contained within the HBsAg particle. As the applicant's argue, the particles themselves are described as containing pores through which proteins can permeate the interior space, thus becoming "encapsulated". However, the specification's working examples utilize a soluble protein, OVA, and a soluble peptide, HIV/env/V3. Unlike soluble proteins which are typically hydrophilic or neutral, proteins or peptides with hydrophobic regions would be attracted to the hydrophobic lipid/HBsAg layer, such that instead of entering the particle pores to be contained within the HBsAg layer, the skilled artisan might expect that proteins or peptides with hydrophobic regions would incorporate themselves into the particle layer. As stated in previous office actions, U.S. Patent No. 5,039,522, issued 8/13/91, (hereafter referred to as Neurath) describes just such a phenomenon. Neurath teaches that peptides with hydrophobic tails are absorbed by HBsAg particles (Neurath, column 3). The specification does not provide any guidance as to the physical and chemical conditions under which hydrophobic or insoluble proteins or peptides can be encapsulate into HBsAg particles. Thus, based on the nature of

protein/protein and protein/lipid hydrophobic interactions, the teaching of Neurath et al. that peptides with hydrophobic tails are absorbed by HBsAg particles rather than encapsulated within, and the lack of guidance provided by the specification, the skilled artisan would not have predicted success in making HBsAg particles which encapsulate a hydrophobic or insoluble protein or peptide using the described methodology of incubating the two ingredients in aqueous solution.

Previous office actions further stated that genetics, dose or concentration of antigen, and route of antigen administration contribute to the unpredictability of generating CTL, helper T cell, and/or B cell responses in vivo (Abbas et al. and Golding et al). The prior art teaches that the concentration of antigen significantly affects the development of cellular (Th1) versus humoral(Th2) immune responses such that low antigen concentrations preferentially induce Th1 type responses and high concentrations of antigen induce Th2 type responses (Abbas et al). The antigens themselves have also been reported to affect the type of immune response generated. For example intracellular microorganisms such as Salmonella, Leishmania, Malaria and Listeria typically induce Th1 type responses, whereas schistosomiasis and Nippostongylus typically induce Th2 type responses. A further complicating factor is the genetic background of the infected mammal. The prior art contains numerous reports which demonstrate the Balb/C mice versus C57Bl/6 mice develop different responses to various pathogens. The nature and route of administration of the antigen is also of concern to the generation of a particular T helper phenotype. Golding et al. teaches that intravenous or intraperitoneal immunization leads to

preferential induction of Th1 cells whereas subcutaneous or intramuscular immunization leads to Th2 cells which may be attributable to the participation of various antigen-presenting cells (Golding et al.). Thus, the art at the time of filing clearly teaches that a significant number of variables affect the generation of specific immune responses which render the generation of a particular type of immune response in any mammal unpredictable for any given antigen. In response to these issues, the applicant argues that the claims have been amended to specifically recite the generation of CTL responses. However, this amendment does not overcome the unpredictability of stimulating or modulating a CTL response to any antigen using any route of administration.

Previous office actions also stated that in regards to the incorporation of cytokines or other immunostimulatory proteins in order to increase the immunogenicity of the particles, the specification's working examples only demonstrate increasing CTL responses to HBsAg particles using IL-12, y-IFN, or a bacterial enterotoxin without disclosing the route of administration or the conditions under which the particles are formed. Of particular note, the working examples also demonstrate the unpredictability of identifying cytokines useful for increasing a particular type of immune response based on reported function. IL-2 has been associated in the literature with stimulating CTL responses. However, the specification's working examples show that HBsAg particles encapsulating IL-2 were ineffective in generating an HBsAg CTL response. Thus, in view of the art at the time of filing which teaches that a significant number of variables affect the generation of specific immune responses, the lack of specific guidance in the specification

concerning routes of administration, conditions under which the HBsAg particles are formed, and cytokines and other immunostimulatory molecules useful for generating a particular type of immune response to an antigen, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed in any host mammal using any HBsAg particle containing any antigen and/or immunostimulatory protein and any route of administration. In response to these issues, the applicant argues that the applicant's lack of success using HBsAg particles containing IL-2 does not negate enablement. Specifically, the applicant argues that IL-2 protein is unstable at 56°C, citing Kedar et al. which was submitted with applicant's supplemental response. The office acknowledges that Kedar et al. teaches that at temperatures over 50°C, IL-2 loses the majority of its biological activity. However, the specification teaches that 56°C is the optimal temperature for preparing protein containing HBsAg particles. Figure 3 shows that the temperature at which the particles are incubated significantly affects the amount of peptide incorporated, with the largest amount incorporated at 56°C. At temperatures less than 56°C, i.e. 37°C, or 4°C, less than half the amount of protein is encapsulated in the HbsAg particles. Thus, for proteins which as a result of lower melting temperatures require incubation at temperatures less than 56°C, the skilled artisan would not be able to predict whether the amount of protein incorporated would be sufficient to modulate any type of immune response, or a CTL response in particular. Neither the prior art of record, not applicant's specification provides any guidance as to the level of cytokine required to modulate a CTL response in vivo. Thus, the teachings of Kedar et al. only serve to provide a rational of why applicants experiments with IL-2 were a

failure, and do not supplement the specification so as to provide an enabling disclosure for the use of any and all immunostimulatory cytokines in the disclosed methods.

In response to the lack of enablement for treating any and all diseases by stimulating CTL responses, in particular viral disease such as HBV or HIV, the applicant argues that the claims have been amended to recite methods of stimulating a CTL response. However, as stated in previous office actions, the specification clearly teaches that the purpose of stimulating an immune response such as a CTL response is for vaccination against infectious organisms such as viruses or bacteria (specification page 2). The specification does not provide any reason for stimulating a CTL response using the disclosed particles other than for protecting or treating infection. The previous office actions have provided evidence in the form of teachings by Yasutomi et al. and Fox et al. that the skilled artisan at the time of filing did not consider the generation of CTL responses as correlative of disease treatment, particularly viral disease. Thus, for the reasons outlined above and in previous office actions, applicant's arguments do not overcome the rejection of record.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 5-6, 11, 17-18, 25-27, and 29-30 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,039,522 (Neurath et al) is withdrawn in view of applicant's amendments to the claims.

The rejection of claims 1-2, 5-7, 11-12, 17-19, and 21 under 35 U.S.C. 102(b) as being anticipated by Michel et al. is withdrawn in view of applicant's amendments to the claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The

technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER